

Research report

Peripheral electric stimulation attenuates the expression of cocaine-induced place preference in rats

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Abstract

The present study was designed to investigate the effect of peripheral electrical stimulation (PES), with high (100 Hz) or low (2 Hz) frequencies, on the expression of cocaine-induced conditioned place preference (CPP). Rats were trained with cocaine (0.1–10 mg/kg, i.p.) under a biased paradigm in a three-compartment chamber for the development of a CPP. One day following the last conditioning, the total time spent in each compartment was recorded after the deliverance of PES. Naloxone (1, 5, and 10 mg/kg, i.p.) was applied to investigate whether endogenous opioid receptor pathways play any role in the effect of PES. It was found that (1) 1 mg/kg and higher doses of cocaine, but not 0.5 mg/kg, produced significant place preference, (2) cocaine-induced CPP, once developed, maintained for more than 13 days in a cocaine-free state, (3) PES of 100 Hz, but not 2 Hz, significantly attenuated the expression of cocaine-induced CPP ($P < 0.01$), (4) PES per se did not influence the natural place preference in rats, and (5) the inhibition of cocaine CPP induced by 100 Hz PES could be reversed by naloxone pre-treatment at 10 mg/kg, but not at lower doses. These results suggest that PES could inhibit cocaine-induced CPP in a frequency-dependent manner. This effect is probably mediated by an endogenous κ -opioid mechanism. © 2002 Elsevier Science B.V. All rights reserved.

Theme: Neural basis of behavior

Topic: Drugs of abuse: cocaine

Keywords: Reward; Craving; Conditioned place preference; Peripheral electric stimulation; Cocaine; Opioid

1. Introduction

It has been reported that the incidence of cocaine addiction overrides that of heroin in many countries. The high recurrence rate of cocaine abuse has prompted research for new approaches, pharmacological or non-pharmacological, to suppress the craving for cocaine. It has been well established that the rewarding effects of cocaine are closely associated with the increase of dopamine in mesolimbic and corticostriatal pathways [1,19]. Medications and other approaches that inhibit dopamine transmission might have potential for the treatment of cocaine addiction.

A variety of studies have shown that there is an interaction between the endogenous opioid system and the

dopamine system. Activation of opioid receptors can modulate dopamine release, e.g. activation of μ and δ receptors caused an increase in dopamine release, while activation of κ receptors produced a decrease in dopamine release [23,30]. In addition, opioid receptor antagonists [2,16,20] and agonists [21] have been shown to attenuate the rewarding effects of cocaine in several different animal models. These results suggested that the endogenous opioid system may be involved in mediating or modulating the rewarding effect of cocaine. Since PES was reported to have the ability to activate endogenous opioid system, it would be interesting to examine the effect of PES on cocaine reward.

PES has now been employed as a treatment of numerous disorders. It is developed on the basis of traditional Chinese medicine, and has been shown to be able to exert various effects in modulating the central nervous system. For example, it can enhance the release and biosynthesis of neurotransmitters, and modulate neuronal gene expression

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[1,10]. The acupoint ST36 and SP6 are commonly used stimulation points. They have been proved effective in the induction of analgesia [10], the amelioration of withdrawal syndrome in heroin addicts [9,31,32], and the attenuation of drug craving in morphine-conditioned rats [29]. What attracts us most is that PES depressed morphine-induced CPP in a frequency-dependent manner [29]. It is suggested that PES inhibits the morphine-induced CPP through an interaction between endogenous dopamine system and endogenous opioid system. Thus, it would be interesting to extend the study of PES to the treatment of cocaine addiction. The current research was designed to evaluate the effects of PES (via ST36 and SP6 acupoints) on the expression cocaine-induced CPP in rats. Our working hypothesis was that PES might exert its effect also by the activation of endogenous opioid systems.

Most of the drugs abused in human beings produce CPP in animals [9]. Thus, CPP has become a widely used animal model to study the rewarding properties of abused substances such as cocaine, amphetamine, and opiates [15,26]. In the current study, a CPP paradigm was used to evaluate the anti-craving effect of PES.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (Institute of Animal Research, Chinese Academy of Science, Beijing), weighing 180–200 g at the beginning of the experiment, were used in the whole study. They were housed four per chamber, with the room temperature maintained at 22 ± 1 °C, relative humidity at 50%, and kept under a 12:12-h light/dark cycle. Food and water were available ad libitum. Rats were habituated to the environment and daily handling for 5 days from arrival before the experiment started. The habituation, training, and testing were conducted during the light phase of the cycle. The experimental procedures were approved by the Committee on Animal Care and Use of the Peking University.

2.2. Drugs

Cocaine hydrochloride was purchased from the Pharmaceutical Factory of Qinghai (China), and naloxone HCl from Sigma Co. (USA). All drugs were dissolved in 0.9% saline (NS) to their final concentrations, and intraperitoneal (i.p.) injection was made immediately before the subject was placed in the drug-conditioning chamber.

2.3. Apparatus

The place conditioning apparatus were PVC plastic rectangular chambers ($71.5 \times 36.5 \times 30$ cm) that consisted of three compartments. Two conditioning compartments

(24×35 cm) were separated by a smaller middle one (15.5×19.5 cm). One of the conditioning compartments had white walls and a stainless steel mesh floor (1.3×1.3 cm²), the other had black walls and 'grid' floor, which consisted of stainless-steel rods (1.3 cm apart). The middle chamber had gray walls and a plain gray floor. Animals could access the entire apparatus when the guillotine doors were removed. Through a computer interface, time spent in each chamber was recorded by sets of infrared beams located near the floor of each chamber.

2.4. Place conditioning procedure

The procedure consisted of three phases: pre-conditioning, conditioning and post-conditioning test.

2.4.1. Pre-conditioning

Before the start of the place conditioning, rats were placed in the middle compartment of the chamber with the guillotine doors removed, thus they were given free access to the whole chamber 15 min daily for 3 consecutive days. The time spent in each compartment was recorded on the third day. The compartment occupied for less time was designated as the non-preferred side. The total time spent in the non-preferred side was divided by total time spent in both preferred and non-preferred sides, and the result was taken as the preference score. The expression of any preference in this phase was considered as natural place preference.

2.4.2. Conditioning

The conditioning phase began on the day following the baseline testing. During conditioning, rats were injected with cocaine (i.p.) once every other day and immediately confined to the non-preferred side for 20 min. On alternate days, rats received saline injections and were confined to the preferred side for 20 min. Control animals received saline injections in both conditioning chambers. The conditioning phase was maintained for 8 days. The middle chamber was never used during conditioning and was blocked by guillotine doors.

2.4.3. Post-conditioning test

The next day after the last conditioning trial, animals were placed in the middle compartment with the guillotine doors removed, so that they had free access to the entire chamber for 15 min. The CPP was recorded as the pre-conditioning test.

2.5. Peripheral electric stimulation

Rats were restrained in special holders, with their hind legs and tails exposed [17]. Two stainless-steel needles of 0.3 mm diameter were inserted into each hind leg, one in a place around the acupoint ST36 (5 mm lateral to the anterior tubercle of the tibia), and the other around SP6 (2

mm to the posterior border of the tibia). Constant current square-wave electric stimulation produced by a HANS LH-800 programmed pulse generator (produced by Beijing University of Astronautics and Aeronautics Aviation) was given via the needles for a total of 30 min. The frequency of stimulation used was 2 or 100 Hz. The intensity of stimulation was increased stepwise from 1 mA to 2 and 3 mA, with each step lasting for 10 min. The PES stimulation was given immediately after the last conditioning trial, like other control treatments in this study. The CPP was tested 24 h after the treatment.

2.6. Statistical analysis

Data were processed by commercially available software GraphPad Prism 3.0. Results are presented as mean±S.E.M. Comparisons between means of groups were analyzed with one-way analysis of variance (ANOVA) followed by Student–Newman–Keul's test. The accepted level of statistical significance was $P<0.05$.

3. Results

3.1. Acquisition of cocaine-induced CPP

Four groups of rats, with 12 in each group, were trained through the CPP paradigm with 0.5, 1, 5, and 10 mg/kg of cocaine, respectively. A fifth group of 12 rats was trained with saline as control. The average CPP scores recorded at the testing day were shown in Fig. 1. Rats receiving saline and 0.5 mg/kg cocaine training showed no significant difference from their own natural preference ($P>0.05$). However, animals receiving 1–10 mg/kg cocaine training displayed significantly higher CPP scores than their natural preference ($P<0.001$). Thus, 1 mg/kg and higher doses of cocaine produced a stable CPP with our current paradigm.

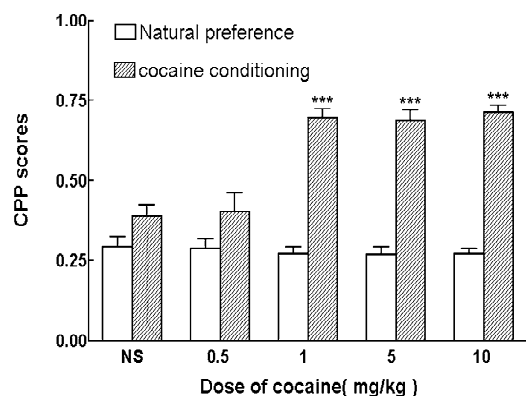


Fig. 1. Expression of CPP induced by different doses of cocaine. *** $P<0.001$, compared with corresponding natural preference (NP). $n=12$.

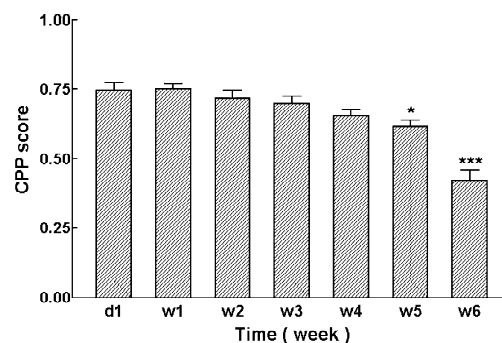


Fig. 2. Maintenance of CPP induced by 5 mg/kg of cocaine. CPP score was tested once a week during drug-free period. * $P<0.05$, *** $P<0.001$, compared with the first day CPP expression (d1). $n=12$.

3.2. Maintenance of the CPP

Two groups of rats, with 12 in each group, were trained with 5 mg/kg of cocaine. One of them was designated for testing CPP maintenance weekly after the post-conditioning testing. The other group was tested daily. CPP score was significantly decreased when tested weekly at the fifth week ($P<0.05$) and the sixth week ($P<0.001$, see Fig. 2). If tested daily, however, the cocaine-induced CPP dropped gradually, and began to show significant difference since the 14th day compared with the first day (Fig. 3).

3.3. Effect of PES on the CPP

To test the effect of PES of different frequencies on cocaine-induced CPP expression, six groups of rats were conditioned with 5 mg/kg of cocaine. On the post-conditioning test phase, group 1 received no treatment. Groups 2, 3, and 4 either received needle insertion without electric stimulation, was merely restrained in the holder, or was given foot shock, respectively. PES of 2 or 100 Hz was given to groups 5 and 6. All groups were tested for their CPP expression 24 h after the treatment. The results were shown in Fig. 4. Only 100 Hz PES significantly decreased

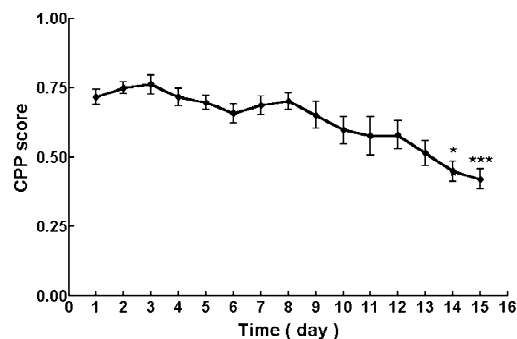


Fig. 3. Maintenance of the cocaine-induced CPP under daily repeated testing. CPP score was tested daily during drug-free period. ** $P<0.01$, *** $P<0.001$, compared with the CPP expression at the first day. $n=12$.

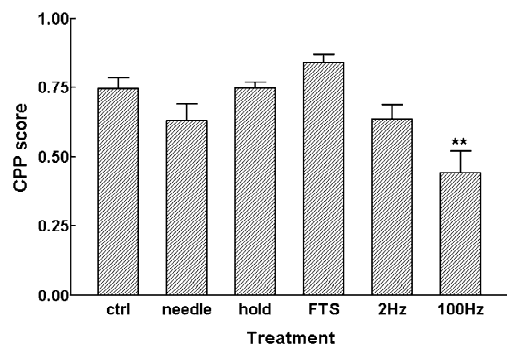


Fig. 4. Effect of PES of different frequencies on CPP expression induced by 5 mg/kg of cocaine. PES of 2 and 100 Hz, respectively, were given 24 h before CPP testing, with no treatment (ctrl), pure needling (needle), restrain (hold), and footshock (FTS) as different controls. ** $P < 0.01$, compared with NS or no-treatment group. $n = 12$.

the expression of the cocaine-induced CPP ($P < 0.01$, compared with the control group).

3.3.1. Effects of 100 Hz PES on CPP expression induced by different doses of cocaine

Three groups of rats, with 24 in each group, were conditioned with 1, 5 or 10 mg/kg of cocaine respectively. At the post-conditioning test phase, each group was evenly divided into two sub-groups, and were given 100 Hz PES or no treatment as control. They were tested for their CPP expression 24 h after the treatment. As shown in Fig. 5, the CPP scores in rats trained with all doses were significantly decreased after PES ($P < 0.01$ for the dose of 1 and 5 mg/kg, and $P < 0.05$ for the dose of 10 mg/kg, compared with corresponding control).

3.3.2. Time course of the effects of 100 Hz PES on CPP expression

Two groups of rats, with 12 in each, were conditioned with 5 mg/kg of cocaine. At the post-conditioning test phase, one of them were given 100 Hz PES, and tested for the CPP expression at 5, 10, 24 and 48 h, respectively,

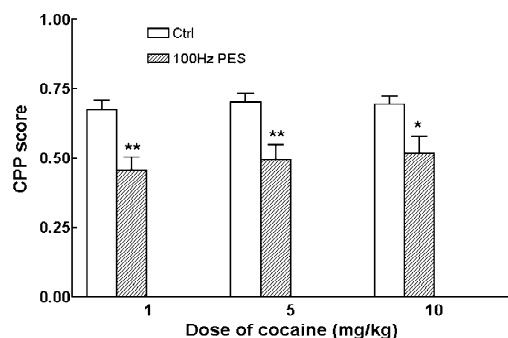


Fig. 5. Effect of 100 Hz PES on CPP expression induced by different doses of cocaine. One hundred Hertz PES was given 24 h before the CPP testing. * $P < 0.05$, ** $P < 0.01$, compared with corresponding controls. $n = 12$.

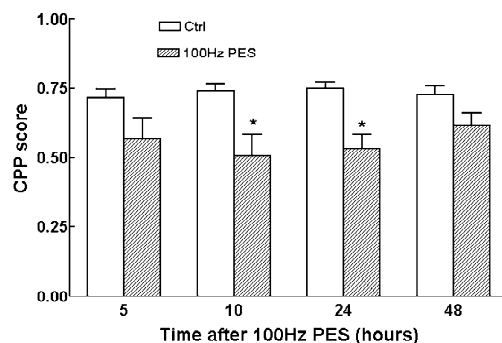


Fig. 6. Time course of attenuation of cocaine-CPP by PES. ** $P < 0.01$, compared with the corresponding control. $n = 12$.

after the PES treatment. Another group was used as control without any treatment. As shown in Fig. 6, the CPP scores obtained from 10 to 24 h were significantly decreased ($P < 0.01$, compared with that of the control), suggesting that the attenuating effect of 100 Hz PES on cocaine-induced CPP may need at least 5 h for onset and may last as long as a whole day. The CPP score at the 48-h point was not significantly influenced ($P < 0.05$, compared with that of control), suggesting that expression of cocaine CPP was restored.

3.4. Effect of 100 Hz PES on natural preference

Three groups of rats, with 12 in each, were conditioned with NS. At the post-conditioning test phase, two of them were given 100 or 2 Hz PES, respectively. The other one was used as control with no treatment. CPP expression was tested 24 h after the PES treatment. As shown in Fig. 7, PES has no significant influence on natural preference ($P > 0.05$).

3.5. Effects of naloxone on CPP attenuation by 100 Hz PES

Four groups of rats, with 12 in each, were conditioned

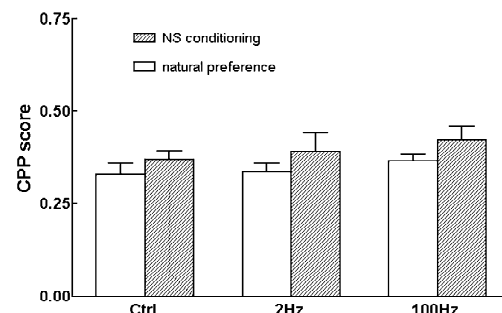


Fig. 7. Effect of different frequencies of PES on natural preference. The rats were injected saline i.p. throughout the conditioning period. At the post-conditioning test stage, PES of 2 and 100 Hz, respectively, were given 24 h before the CPP testing. $n = 12$.

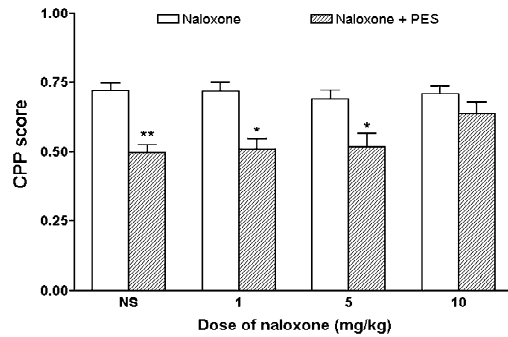


Fig. 8. Naloxone reversed the CPP-attenuating effect of 100 Hz PES. In the naloxone group, different doses of naloxone (0–10 mg/kg) were injected 24 h after the last conditioning trial. CPP was again tested 24 h after naloxone was given. In the naloxone+PES group, 100 Hz PES was given 24 h after the last conditioning trial. Naloxone was injected 20 min before the PES was given, while CPP was tested 24 h after the PES treatment. * $P < 0.05$, ** $P < 0.01$, compared with the NS alone treatment group. $n = 12$.

with 5 mg/kg of cocaine. At the post-conditioning test phase, they were given saline, or 1, 5, or 10 mg/kg of naloxone, respectively, 20 min before 100 Hz PES. The expression of CPP was tested 24 h after the PES treatment. As shown in Fig. 8, naloxone reversed the effect of PES on the CPP expression only at the dose of 10 mg/kg ($P > 0.05$, compared with the CPP scores in the pre-conditioning phase), but not at lower doses.

To observe effect of naloxone alone on cocaine CPP, another four groups of rats, with 12 in each, were conditioned with 5 mg/kg of cocaine. At the post-conditioning test phase, they were given saline, 1, 5, or 10 mg/kg of naloxone, respectively. CPP score was then tested 30 min and again 24 h after naloxone treatment. The result showed that cocaine CPP was suppressed by 5 and 10 mg/kg, but not saline and 1 mg/kg, of naloxone at the 30-min point (data not shown). At the 24-h point, no doses of naloxone influenced cocaine CPP (see Fig. 8).

4. Discussion

Conditioned place preference is based on the principle that when a primary reinforcer (e.g. a drug) is paired with contextual neutral stimuli (e.g. the condition in which the subject is reinforced), the contextual stimuli can acquire conditioned reinforcing properties. Therefore a drug-induced CPP is thought to be able to mimic the cue-elicited conditioning that motivates drug-seeking behavior [15]. Thus, the CPP paradigm has been widely used to study the reinforcing effects of addictive drugs [18]. Previous studies have shown that the establishment of cocaine-induced CPP depends on the dose and route of administration as well as the number of conditioning sessions used [18]. In the present study, we employed an 8-day conditioning paradigm, and reliable place preference could be developed

with cocaine (i.p.) at 1 mg/kg and higher doses. Once acquired, the expression of cocaine-induced CPP maintained as long as 4 weeks at weekly checking or 13 days at daily checking extinction schedule. This is in agreement with previous reports [15,18] that repeated exposure to the previously drug-paired environment in the absence of the drug will accelerate the extinction of established conditioning.

PES has been proved to be effective in abolishing the expression of morphine-induced CPP in rats [29]. As reported before, the PES procedure might involve three stressor components: restraining, needling, and electric shocking. To control these factors, we set three corresponding control groups, where electric shocking was mimicked by foot shock stimulation. The results (Fig. 4) showed that none of them had any significant effect on the place preference induced by cocaine. Even 2 Hz PES, placed at the same sites of the stimulation, was not effective in reducing the cocaine CPP (Fig. 4). These results suggested that it was the specific parameters of PES rather than a non-specific stressful condition that played an important role in modulating cocaine CPP. The importance of the PES parameter was also stressed by the fact that it was 2 Hz, but not 100 Hz PES, that was effective in modulating morphine-induced CPP [29].

PES of identified frequencies had been proved to mobilize different kinds of endogenous opioid peptides, which in turn act on their corresponding receptors to induce analgesia. According to the previous studies in our laboratory [4,7], PES of 2 Hz could increase the release of enkephalin in brain to interact with μ - and δ -opioid receptors, while PES of 100 Hz could increase the release of dynorphin in spinal cord, which interacts with κ -opioid receptors. A logical reason would imply that the attenuation of cocaine CPP by 100 Hz PES may involve a κ -opioid mechanism.

It has been reported that κ agonists could attenuate cocaine-induced increase of extracellular dopamine in the nucleus accumbens of rats [17,24], prevent sensitization to the rewarding effects of cocaine [25], and attenuate cocaine self-administration in rats [22]. The relevance of dynorphin/ κ mechanism in the present study was further supported by the fact that the effect of the PES on cocaine-induced CPP could be reversed by naloxone only at a relatively high dose (10 mg/kg). This dose was sufficient to antagonize all three subtypes of opioid receptors [6], including κ . On the other hand, the lower doses (1 and 5 mg/kg), which were only able to inactivate μ - and δ -opioid receptors, could not block the effect of PES.

In the current study, naloxone given 30 min before testing on the post-conditioning day inhibited the expression of cocaine-induced CPP. This result was consistent with another report [5]. However, 24 h after acute naloxone treatment, the expression of cocaine CPP was completely restored. Thus, CPP was specifically decreased by

100 Hz PES, and naloxone seemed to inhibit the initiation of this effect. Though we speculated a κ involvement by evidence that high dose of naloxone reversed PES effect, the exact mechanism remains unclear and needs further experiments.

One of the possibilities for 100 Hz PES inhibiting cocaine CPP was that the activation of κ -receptor-induced amnesia. Previous reports showed that dynorphin improve amnesia-induced β -amyloid peptide [12], scopolamine and pirenzepine [27,28], and carbon monoxide [13]. U50488, a selective κ -opioid receptor agonist, improves carbon monoxide-induced delayed amnesia [11] and prevents memory dysfunctions induced by transient cerebral ischemia in mice [14]. The anti-amnesic effect of dynorphin and U50488 could be reversed [11,13,14,27,28] or partly reversed [12] by nor-BNI, a selective κ -opioid receptor antagonist. These results suggested that the activation of κ receptor could mostly prevent rather than cause the amnesia. We concluded that the inhibition of cocaine CPP was probably not due to amnesia. Hence it might be due to inhibition of cocaine reward.

Taken together, we infer that 100 Hz PES could decrease cocaine-induced CPP, probably via the activation of κ -opioid receptors, thus to attenuate the cocaine reward. PES therefore might be beneficial to the inhibition of cocaine craving in cocaine addicts.

We also found in this study that the effect of PES could exist even 24 h after a single stimulation was given. We have demonstrated before that PES also facilitates the biosynthesis of endogenous opioid peptides. The production of preprodynorphin mRNA in rat brain maintained a high level at 24 h after 100 Hz PES was given [8], which might mediate the long-term (24 h) CPP inhibition.

The neurotransmitters activated by PES are not limited to the endogenous opioid system. It was reported that PES could also activate other transmitters such as cholecystokinin, norepinephrine, dopamine, serotonin, etc. [3]. To further verify whether the PES-induced inhibition of cocaine CPP is mediated by a κ -receptor mechanism, and to explore the possible roles played by other transmitters, further pharmacological experiments are necessary.

5. Conclusion

Cocaine-induced CPP can be suppressed by PES in a frequency-dependent manner, being effective at 100 Hz, but not at 2 Hz. The effect of 100 Hz PES could be reversed by naloxone at 10 mg/kg, but not at 0.1 or 1 mg/kg doses, suggesting the involvement of κ -opioid mechanism in mediating PES effects. These results may infer a clinical implication to reduce cocaine craving and to prevent relapse after abstinence with 100 Hz transcutaneous electric nerve stimulation.

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